Gardasil® Update: Men (Protocol 020)

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Agenda

- Protocol 020 overview
- Efficacy
  - External genital lesions (EGL) endpoint
  - Anal intra-epithelial neoplasia (AIN) endpoint
  - AIN case assignment analysis
  - Persistent anal HPV infection (6-month) endpoint
  - AIN intention-to-treat analyses
- Immunogenicity
- Safety
- Conclusions

Men – Protocol 020
Overview

- Design:
  - Randomized, double-blind, placebo-controlled, international, multicenter study
- Subjects:
  - Heterosexual men [HM] (N=3463)
  - Men having sex with men [MSM] (N=602)
- Objectives:
  - Safety
  - Immunogenicity
  - Efficacy: Primary- HPV 6/11/16/18-related
    - External genital lesions (EGL]) [HM + MSM]
    - Anal intra-epithelial lesions (AIN) [MSM only]

Men – Protocol 020
Why Study MSM?

- MSM have high incidence rates of anal HPV infection
  - Allows for feasibility of a disease endpoint efficacy study
- However:
  - Anal HPV infection occurs in both men and women
  - Anal cancer rates have been increasing in both men and women
  - Pathophysiology of HPV infection/disease of the anal canal is similar in both men and women
- Therefore:
  - Efficacy results of MSM AIN study can be extrapolated to the general population of men and women

Analysis Populations

- **Per Protocol Population [PPE] (Primary)**
  - Baseline HPV negative by HPV DNA & Serology to the relevant HPV type
  - HPV DNA negative to the relevant HPV type at M7
  - Received all 3 doses
  - Case counting starts after M7
  - No protocol violations

- **Full Analysis Set [FAS] (Supportive)**
  - All enrolled subjects who received at least one dose of vaccine or placebo
  - Subjects who had at least one follow-up visit
  - Case counting starts after Day 1

EGL Efficacy by Lesion Type

Per Protocol Efficacy Population

Endpoint	GARDASIL (N=2025)		Placebo (N=2030)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related EGL	1394	3	1404	32	90.6	70, 98
Condyloma	1394	3	1404	28	89.3	65, 98
PIN 1 or worse	1394	0	1404	4	100	-52, 100
PIN 1	1394	0	1404	2	100	-435, 100
PIN 2/3	1394	0	1404	2	100	-435, 100

AIN Efficacy by Lesion Type

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related AIN	194	5	208	24	77.5	40, 93
AIN 1	194	4	144	16	73.0	16, 93
AIN 2/3	194	3	208	13	74.9	9, 95

AIN Efficacy by Lesion Type

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related AIN	194	5	208	24	77.5	40, 93
AIN 1	194	4	144	16	73.0	16, 93
AIN 2/3	194	3	208	13	74.9	9, 95

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 16/18-Related AIN 2/3	192	1	205	8	86.6	0.013, 100
By HPV Type						
HPV 16	167	1	170	6	82.8	-41, 100
HPV 18	173	0	193	2	100	-501, 100

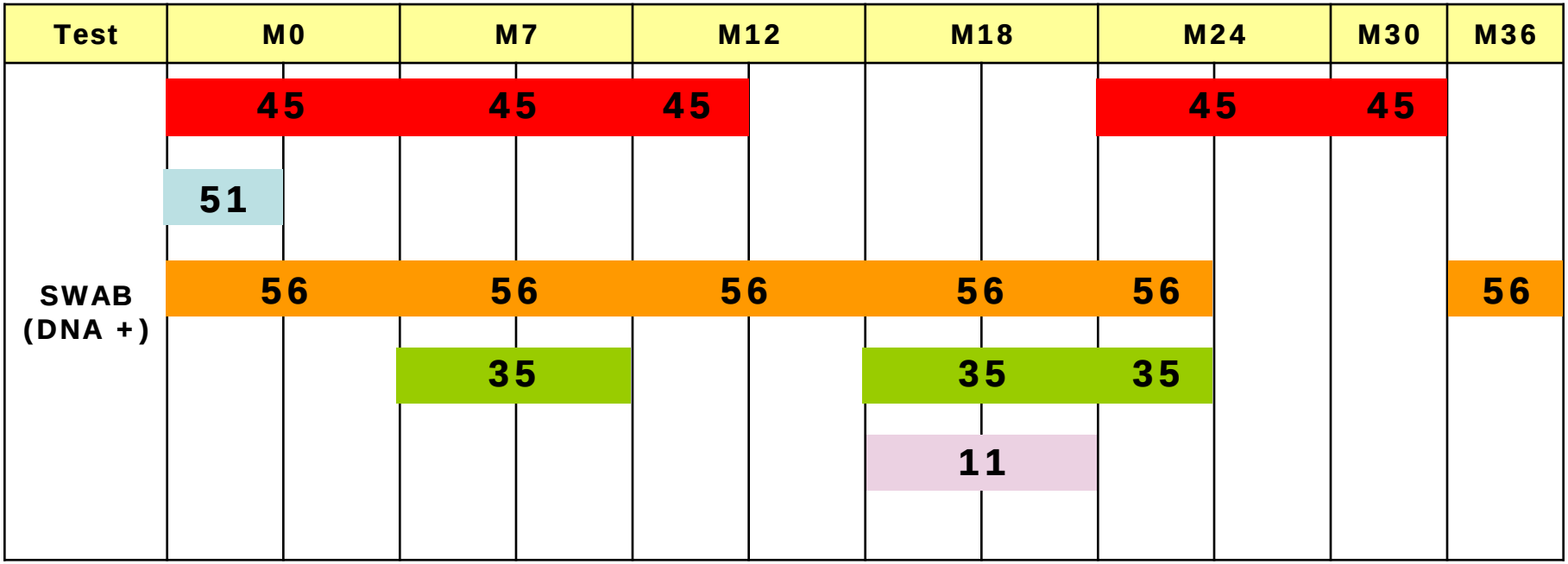
Further Understanding of AIN Efficacy
Clinical Case Assignment Analysis

- How is a vaccine HPV type attributed to an incident AIN lesion?
  - AIN diagnosis by Pathology Panel
  - HPV 6, 11, 16 or 18 by PCR in adjacent section of same tissue block
  - Presence of other non-vaccine HPV types in AIN lesion not considered in primary pre-specified analysis
- However:
  - Anal infection with multiple HPV types is common in MSM
  - Subjects in PPE population were commonly infected at study entry with high-risk non-vaccine HPV types
  - Anal swab positivity for non-vaccine HPV types often preceded development of vaccine-type attributed AIN lesion (in the absence of any evidence of preceding infection with the vaccine type)
- Therefore:
  - Case assignment analysis performed (ad hoc)

Case Assignment Analysis Methodology

- AIN cases where co-infection occurred assessed for evidence of preceding infection with HPV types
  - The two immediately preceding anal swabs evaluated
- HPV type detected in at least one of the two swab samples as well as in the lesion was assigned as causal HPV type
- If none of the HPV types detected in the lesion were found in either of the two immediately preceding swab samples, the lesion was attributed to the lesional HPV type
- Following this case assignment methodology, efficacy analysis performed

Vaccine Group Case of HPV 6-Related AIN 1



Biopsy:
AIN 1 – HPV 6, 35, 56

AIN Efficacy by Lesion Type

AIN HPV Case Assignment Analysis

Per-Protocol Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related AIN	194	2	208	24	91.1	64, 99
AIN 1	194	2	208	16	86.6	43, 99
AIN 2/3	194	1	208	13	91.7	45, 100
AIN 2	194	1	208	9	87.9	13, 100
AIN 3	194	1	208	6	81.9	-49, 100

Efficacy Against HPV 6/11/16/18-Related Anal Persistent Infection (6-months)

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related Anal Persistent Infection	193	2	208	39	94.9	80, 99
By HPV Type						
HPV 6	140	1	144	13	92.1	47, 100
HPV 11	140	0	144	5	100	-16, 100
HPV 16	166	1	170	16	93.8	60, 100
HPV 18	172	0	193	10	100	52, 100

Analysis of Efficacy Against AIN in FAS‡ Populations

Endpoint	GARDASIL (N=299)	Placebo (N=299)	Observed Efficacy (%)	95% CI
Any HPV Type-related AIN	74	103	25.7	-1, 46
AIN 1	54	79	30.0	-0.2, 51
AIN 2/3	44	59	24.3	-14, 50
HPV 6/11/16/18-related AIN*	38	77	50.3	26,67
AIN 1	31	62	49.6	21, 68
AIN 2/3	18	39	54.2	18, 75
Non-vaccine HPV-related AIN (10 types)†	38	44	11.8	-39, 44
AIN 1	23	28	16.6	-50, 54
AIN 2/3	24	24	-2.7	-89, 44

‡ FAS – all subjects enrolled, case counting after Day 1, regardless of baseline HPV status

* Baseline MSM HPV 6/11/16/18 status:
  - serology – 22.8%, PCR – 30.5%, serology and PCR – 39.1%

† Non-vaccine HPV-related AIN (10 types) – 31/33/35/39/45/51/52/56/58/59

Summary of Peak Response Anti-HPV GMTs Among Males 16-26 Years of Age

Per-Protocol Immunogenicity Population

HPV Type	GARDASIL (N=2025)			
	GMT[1]	95% CI	SCR[2]	95% CI
Anti-HPV 6 Month 7	447.0	422, 474	98.9	98, 99
Anti-HPV 11 Month 7	624.2	594, 656	99.2	98, 100
Anti-HPV 16 Month 7	2402.5	2271, 2542	98.8	98, 99
Anti-HPV 18 Month 7	402.2	380, 426	97.4	96, 98

1. GMT – geometric mean titers
2. SCR – seroconversion rate

Summary of Anti-HPV GMT Among Subjects 16-26 Years of Age Vaccinated with GARDASIL®

Per-Protocol Immunogenicity Population

HPV Type	Males (N=2025)		Females (N=9885)	
	GMT[1] (mMU/mL)	95% CI	GMT[1] (mMU/mL)	95% CI
Anti-HPV 6 Month 7	447.0	422, 474	545.2	528, 563
Anti-HPV 11 Month 7	624.2	594, 656	749.0	726, 773
Anti-HPV 16 Month 7	2402.5	2271, 2542	2411.3	2312, 2515
Anti-HPV 18 Month 7	402.2	380, 426	475.6	458, 494

1. GMT – geometric mean titers

Summary of Anti-HPV GMT Among Subjects 16-26 Years of Age Vaccinated with GARDASIL®

Per-Protocol Immunogenicity Population

HPV Type	Heterosexual Males (N=1726)		MSM Males (N=299)	
	GMT[1] (mMU/mL)	95% CI	GMT[1] (mMU/mL)	95% CI
Anti-HPV 6 Month 7	473.9	447, 503	272.1	221, 335
Anti-HPV 11 Month 7	651.5	621, 684	434.1	351, 537
Anti-HPV 16 Month 7	2622.1	2485, 2767	1269.4	996, 1619
Anti-HPV 18 Month 7	439.3	416, 464	212.8	171, 265

1. GMT – geometric mean titers

Relevance of Immune Responses

- Robust immune response seen in all populations studied
  - ~100% seroconversion rates
  - High GMTs, well above levels seen after natural infection
- High efficacy demonstrated against disease endpoints across a wide range of GMT levels
- No immune correlate has been identified
- Differences in GMT levels have limited clinical relevance

Adverse Experience (AE) - All Subjects

Entire Study Period

	GARDASIL (N=2020)		Placebo (N=2029)	
	n	**(%)**	**n**	**(%)**
Subjects with follow-up	**1945**		**1950**	
Number (%) of subjects:				
with one or more adverse experiences	**1346**	**(69.2)**	**1252**	**(64.2)**
injection-site adverse experiences	1169	(60.1)	1047	(53.7)
systemic adverse experiences	617	(31.7)	622	(31.9)
with vaccine-related adverse experiences	**1242**	**(63.9)**	**1134**	**(58.2)**
injection-site adverse experiences	1169	(60.1)	1046	(53.6)
systemic adverse experiences	275	(14.1)	283	(14.5)
with serious adverse experiences	**8**	**(0.4)**	**11**	**(0.6)**
with serious vaccine-related adverse experiences	**0**	**(0.0)**	**0**	**(0.0)**
who died	**3**	**(0.2)**	**10**	**(0.5)**

Overall Conclusions

- High efficacy of GARDASIL® demonstrated against HPV 6/11/16/18-related persistent infection and disease (high-grade and low-grade) at multiple anogenital sites
  - Cervical
  - Vulvar
  - Vaginal
  - Anal
  - Genital warts
- High efficacy demonstrated:
  - At both mucosal and keratinized epithelial sites, and
  - In both women and men

- Pathophysiology of persistent infection of HPV at the basal keratinocyte of stratified squamous epithelia is similar regardless of tissue
- Consistently high vaccine efficacy across all tissue sites